

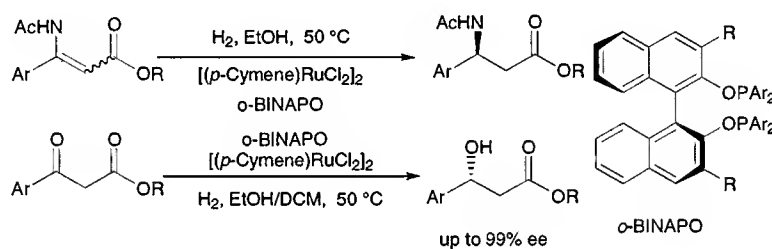
Communication

Highly Effective Chiral Ortho-Substituted BINAPO Ligands (o-BINAPO): Applications in Ru-Catalyzed Asymmetric Hydrogenations of β -Aryl-Substituted β -(Acylamino)acrylates and β -Keto Esters

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Highly Effective Chiral Ortho-Substituted BINAPO Ligands (*o*-BINAPO): Applications in Ru-Catalyzed Asymmetric Hydrogenations of β -Aryl-Substituted β -(Acylamino)acrylates and β -Keto Esters

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During the last several decades, many effective chiral bisphosphines have been developed. However, there is no solution in dealing with many transition metal-catalyzed asymmetric transformations since enantioselectivities are often substrate-dependent. Subtle changes in conformational, steric, and electronic properties of chiral ligands can lead to dramatic variations of reactivities and enantioselectivities. Conformationally rigid and tunable chiral ligands offer a great advantage for optimizing the enantioselectivity of a reaction. Herein, we like to report ruthenium catalysts with a novel family of BINOL-derived phosphinite ligands for the first highly enantioselective hydrogenation of β -aryl-substituted β -(acylamino)acrylates. These catalysts are also effective for highly enantioselective hydrogenation of β -aryl-substituted β -keto esters.

Noyori and co-workers have demonstrated that highly skewed BINAP was an effective ligand for many asymmetric catalytic reactions.^{1,2} A comparison of the structure of BINAP with the less-effective BINAPO ligands³ reveals two possible reasons: (1) the oxygen atoms in the BINAPO increase the distance between the chiral binaphthyl moiety and PPh₂ groups and therefore decrease the influence of chiral binaphthyl on orientation of the phenyl groups of PPh₂ and (2) the presence of the C–O–P bond in BINAPO increases the flexibility of backbone. To develop highly effective BINAPO ligands, we have designed ligands **2a–d** by introducing groups into 3,3'-positions of the binaphthyl backbone (ortho-substituted BINAPO, abbreviated as *o*-BINAPO): introduction of 3,3'-R groups can restrict the orientation of Ar groups adjacent to phosphine atoms. In addition, tuning of the steric and electronic properties can be achieved by changing the R and Ar groups of ligands. These ligands can be synthesized from the corresponding diols **1** (Scheme 1).

Enantiomerically pure β -amino acids and their derivatives are important building blocks for the synthesis of β -peptides, β -lactam antibiotics, and many important drugs.⁵ Recently, several synthetic methodologies have been developed to make β -amino acids by using stoichiometric chiral auxiliaries and catalytic methods.⁶ Among these methods, straightforward asymmetric hydrogenation of β -aminoacrylic acid derivatives represents one of the simplest routes. Previous attempts at asymmetric hydrogenation of β -(acylamino)acrylates using Ru⁷ and Rh⁸ catalysts led to moderate to good enantioselectivity. The main issue is that the different catalytic behaviors (ee values, catalytic activities) exist with *Z*- and *E*-isomeric substrates. For example, (*E*)-methyl 3-acetamido-2-butenate gave 96% ee in Noyori's Ru-BINAP system,⁷ while (*Z*)-methyl 3-acetamido-2-butenate gave only 5% ee with the opposite configuration. So far, only moderate ee can be obtained with Rh-

Scheme 1

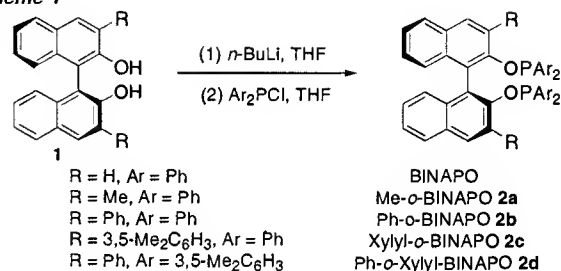


Table 1. Asymmetric Hydrogenation of β -Aryl-Substituted β -(Acylamino)acrylates **3**^a

entry	ligands	Ar of 3	R of 3	ee (%) ^b	config. ^c
1	BINAPO	Ph	Me (3a)	2 (5a)	S
2	2a	Ph	Me (3a)	22 (5a)	S
3	2b	Ph	Me (3a)	98 (5a)	S
4	2c	Ph	Me (3a)	99 (5a)	S
5	2d	Ph	Me (3a)	97 (5a)	S
6	BINAP	Ph	Me (3a)	31 (5a)	S
7	MeO-Biphep	Ph	Me (3a)	39 (5a)	S
8	2c	<i>p</i> -F-C ₆ H ₄	Me (3b)	99 (5b)	S
9	2c	<i>p</i> -Cl-C ₆ H ₄	Me (3c)	97 (5c)	S
10	2c	<i>p</i> -Br-C ₆ H ₄	Me (3d)	97 (5d)	S
11	2c	<i>p</i> -Me-C ₆ H ₄	Me (3e)	99 (5e)	S
12	2c	<i>p</i> -MeO-C ₆ H ₄	Me (3f)	99 (5f)	S
13	2c	<i>o</i> -Me-C ₆ H ₄	Me (3g)	96 (5g)	S
14	2c	<i>o</i> -MeO-C ₆ H ₄	Me (3h)	80 (5h)	S
15	2c	Ph	Et (3i)	98 (5i)	S
16	2c	<i>p</i> -F-C ₆ H ₄	Et (3j)	98 (5j)	S
17	2c	<i>p</i> -Cl-C ₆ H ₄	Et (3k)	95 (5k)	S
18	2c	<i>p</i> -Br-C ₆ H ₄	Et (3l)	93 (5l)	S

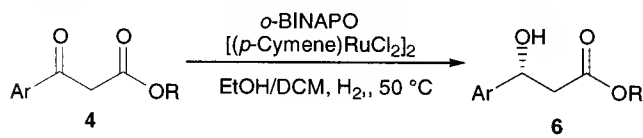
^a The absolute configurations were determined by comparing optical rotations with reported values. The reaction was carried out under 80 psi of H₂ in EtOH at 50 °C for 20 h, substrate/[Ru(*p*-cymene)Cl₂]₂/ligand = 50/1/2.1. ^b The ee (%) values were determined by GC using a chiralselect 1000 column. ^c Determined by the sign of rotations.

DuPhos^{8c} and Ru-BINAP⁷ systems for hydrogenation of β -aryl-substituted β -(acylamino)acrylates.

To test the synthetic utility of bisphosphinite ligands **2**, we have explored the Ru-catalyzed asymmetric hydrogenation of β -aryl-substituted β -(acylamino)acrylates **3** (Table 1). Substrates **3a–l** (*E/Z* = 5/95 to 40/60) can be made from the β -keto esters **4** according to a literature procedure.^{8c,9} The *E/Z* mixture of enamides **3a–l** cannot be separated by silica gel column chromatography. The Ru catalyst was prepared by mixing the [Ru(*p*-cymene)Cl₂]₂ and a

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Table 2. Asymmetric Hydrogenation of β -Keto Esters **4**^a

					
entry	ligand	Ar of 4	R of 4	ee (%) of 6 ^b	config. ^c
1	2c	Ph	Et (4a)	99 (6a)	R
2	2c	<i>p</i> -F-C ₆ H ₄	Et (4b)	93 (6b)	R
3	2c	<i>p</i> -Cl-C ₆ H ₄	Et (4c)	98 (6c)	R
4	2c	<i>p</i> -Br-C ₆ H ₄	Et (4d)	96 (6d)	R
5	2c	<i>p</i> -Me-C ₆ H ₄	Et (4e)	95 (6e)	R
6	2c	<i>p</i> -MeO-C ₆ H ₄	Et (4f)	87 (6f)	R
7	2c	<i>o</i> -Me-C ₆ H ₄	Et (4g)	90 (6g)	R
8	2c	<i>o</i> -MeO-C ₆ H ₄	Et (4h)	98 (6h)	R
9	2d	Me	Me (4i)	96 (6i)	S
10	2d	Me	Et (4j)	96 (6j)	S
11	2d	ClCH ₂	Et (4k)	98 (6k)	R

^a The absolute configurations were determined by comparing optical rotations with reported values. The reaction was carried out under 80 psi of H₂ in EtOH/DCM (3/1) at 50 °C for 20 h, substrate/[Ru(*p*-cymene)Cl₂]₂/ligand = 200/1/2.1. ^b The ee (%) values were determined by GC using a Chiralselect 1000 column or HPLC with Chiralpak AS column. ^c Determined by the sign of rotations.

bisphosphinite ligand **2** in situ in hot DMF.¹⁰ The reaction was carried out under 80 psi of H₂ in EtOH at 50 °C for 20 h. Although ligands BINAPO and **2a–d** show similar reactivity, the enantioselectivity varied dramatically. For example, substrate **3a** was reduced with 2% ee using a Ru-BINAPO complex as the catalyst (entry 1). The enantioselectivity increased to 22% with Ru-Me-*o*-BINAPO (**2a**) (entry 2). Surprisingly, ee values increased dramatically when an aryl was introduced in the *o*-BINAPO ligand (entries 3–5). Up to 99% ee has been achieved with the Ru-**2c** catalyst (entry 4). This result is superior to ee values obtained with other phosphine ligands (entry 6, 31% ee with BINAP; entry 7, 39% ee with MeO-BIPHEP).

A variety of β -aryl-substituted β -(acylamino)acrylates were employed as substrates for the Ru-catalyzed hydrogenation reaction with **2c** as the ligand (Table 1). High enantiomeric excesses have been achieved with the exception of **3h** (entry 14). There is no major electronic effect on the substitution pattern of **3** (96–99% ee). A possible explanation of the low ee (80%) with *o*-methoxy-substituted enamide **3h** is that competing coordination of the *o*-methoxy group exists in the Ru system. In this catalytic system, methyl β -aryl-substituted β -(acylamino)acrylates gave slightly better enantioselectivities than the corresponding ethyl β -aryl-substituted β -(acylamino)acrylates.

It is noteworthy that our catalytic system Ru-bisphosphinite can tolerate an *E/Z* mixture of substrates. The ability to reduce the *E/Z* mixture of β -aryl-substituted β -(acylamino)acrylates **3** is crucial to practical synthesis of various β -aryl-substituted β -amino acids. To the best of our knowledge, enantioselectivities achieved with Ru-**2c** as the catalyst for hydrogenation of **3** are the highest reported to date.

In a related area, Ru-BINAP^{1,2} and other Ru-phosphine systems¹¹ were efficient for reduction of β -alkyl-substituted β -keto esters, but only moderate to good enantioselectivities were obtained for hydrogenation of β -aryl-substituted β -keto esters.

To further expand the utility of the *o*-BINAPO ligands system, we have examined Ru-catalyzed enantioselective hydrogenation of β -aryl-substituted β -keto esters (Table 2). High enantioselectivities

have been achieved with most substrates (93–99% ee) except for **4f** and **4g**. Under the same reaction conditions, we examined the enantioselectivities for hydrogenation of **4a**: BINAP (80% ee), MeO-BIPHEP (88%), BINAPO (29%), **2a** (29%), **2b** (94%), **2c** (99%), and **2d** (97%). The enantioselectivities achieved with Ru-**2c** as the catalyst are the highest reported for substrate **4a**. For hydrogenation of β -alkyl-substituted β -keto esters, we found that *o*-BINAPO (**2d**) is a better ligand (entries 9–11).

In conclusion, we have developed a novel family of chiral bisphosphinite ligands for enantioselective Ru-catalyzed hydrogenation. These catalysts are especially effective for hydrogenation of β -aryl-substituted β -(acylamino)acrylates and β -aryl-substituted β -keto esters. The highly enantioselective hydrogenation provides a useful way to prepare β -aryl-substituted β -amino acids and β -hydroxyl acids. Further studies of other transition metal complexes of these ligands and their applications are in progress.

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Supporting Information Available: Full experimental procedure, GC, HPLC data, and $[\alpha]_D$ values of ligands **2** and hydrogenation products **5** and **6** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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